MT-TL1 gene

mitochondrially encoded tRNA leucine 1 (UUA/G)

Normal Function

The *MT-TL1* gene provides instructions for making a molecule called a transfer RNA (tRNA), which is a chemical cousin of DNA. Transfer RNAs help assemble protein building blocks (amino acids) into functioning proteins. The *MT-TL1* gene provides instructions for making a specific form of tRNA that is designated as $tRNA^{Leu(UUR)}$. During protein assembly, this molecule attaches to the amino acid leucine (Leu) and inserts it into the appropriate locations in the growing protein.

The $tRNA^{Leu(UUR)}$ molecule is present in cellular structures called mitochondria. These structures convert energy from food into a form that cells can use. Within mitochondria, $tRNA^{Leu(UUR)}$ is involved in the assembly of proteins that carry out a series of chemical steps called oxidative phosphorylation. This process uses oxygen, simple sugars, and fatty acids to create adenosine triphosphate (ATP), the cell's main energy source.

In certain cells in the pancreas, called beta cells, mitochondria also play a role in controlling the amount of sugar (glucose) in the bloodstream. In response to high glucose levels, mitochondria help trigger the release of a hormone called insulin. Insulin regulates blood sugar levels by controlling how much glucose is passed from the blood into cells to be converted into energy.

Health Conditions Related to Genetic Changes

Leigh syndrome

maternally inherited diabetes and deafness

At least one mutation in the *MT-TL1* gene causes maternally inherited diabetes and deafness (MIDD). People with this condition have diabetes and sometimes hearing loss, particularly of high tones. Less commonly, affected individuals have problems with their eyes, muscles, heart, or kidneys. The *MT-TL1* gene mutation is the most common mutation in MIDD, involved in 85 percent of cases. It changes a single DNA building block (nucleotide) in the *MT-TL1* gene; the nucleotide adenine is replaced by the nucleotide guanine at position 3243 in the gene (written as A3243G).

The A3243G mutation reduces the ability of $tRNA^{Leu(UUR)}$ to add leucine to proteins that are being assembled, which slows protein production. Researchers believe that the A3243G mutation impairs the ability of mitochondria to help trigger insulin release. In people with MIDD, diabetes results when the beta cells do not produce

enough insulin to regulate blood sugar effectively. Researchers have not determined how the A3243G mutation leads to hearing loss or the other features of MIDD.

mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Several mutations in the *MT-TL1* gene have been identified in people with a condition called mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). This condition is characterized by recurrent severe headaches, muscle weakness (myopathy), hearing loss, stroke-like episodes including a loss of consciousness, seizures, and other problems affecting the nervous system. Most of these mutations change single nucleotides in the gene. The A3243G mutation (described above) is the most common mutation in MELAS. It is responsible for about 80 percent of all MELAS cases. This mutation impairs the ability of mitochondria to make proteins, use oxygen, and produce energy. Researchers have not determined how changes in mtDNA lead to the specific signs and symptoms of MELAS. They continue to investigate the effects of mitochondrial gene mutations in different tissues, particularly in the brain.

myoclonic epilepsy with ragged-red fibers

Mutations in the *MT-TL1* gene have been found in a few people with features of myoclonic epilepsy with ragged-red fibers (MERRF). These individuals also have some features of MELAS (described above). This combination of signs and symptoms is called MERRF/MELAS overlap syndrome. The features of this syndrome include muscle twitches (myoclonus), muscle weakness (myopathy), difficulty coordinating movement (ataxia), hearing loss, seizures, and diabetes.

Mutations that cause MERRF/MELAS overlap syndrome each change single nucleotides in the *MT-TL1* gene. Researchers have not determined how these genetic changes cause the signs and symptoms of MERRF/MELAS overlap syndrome.

progressive external ophthalmoplegia

Mutations in the *MT-TL1* gene are responsible for some cases of an eye condition called progressive external ophthalmoplegia. This disorder weakens the muscles that control eye movement and causes drooping eyelids (ptosis).

Some cases of progressive external ophthalmoplegia result from the A3243G mutation, which is the same genetic change that typically causes MELAS and MIDD (described above). It is unclear how the same *MT-TL1* gene mutation can result in different conditions. Researchers have not determined how changes in mtDNA lead to the specific signs and symptoms of progressive external ophthalmoplegia, although the features of the condition may be related to impaired oxidative phosphorylation. It has been suggested that eye muscles are commonly affected by mitochondrial defects because they are especially dependent on oxidative phosphorylation for energy.

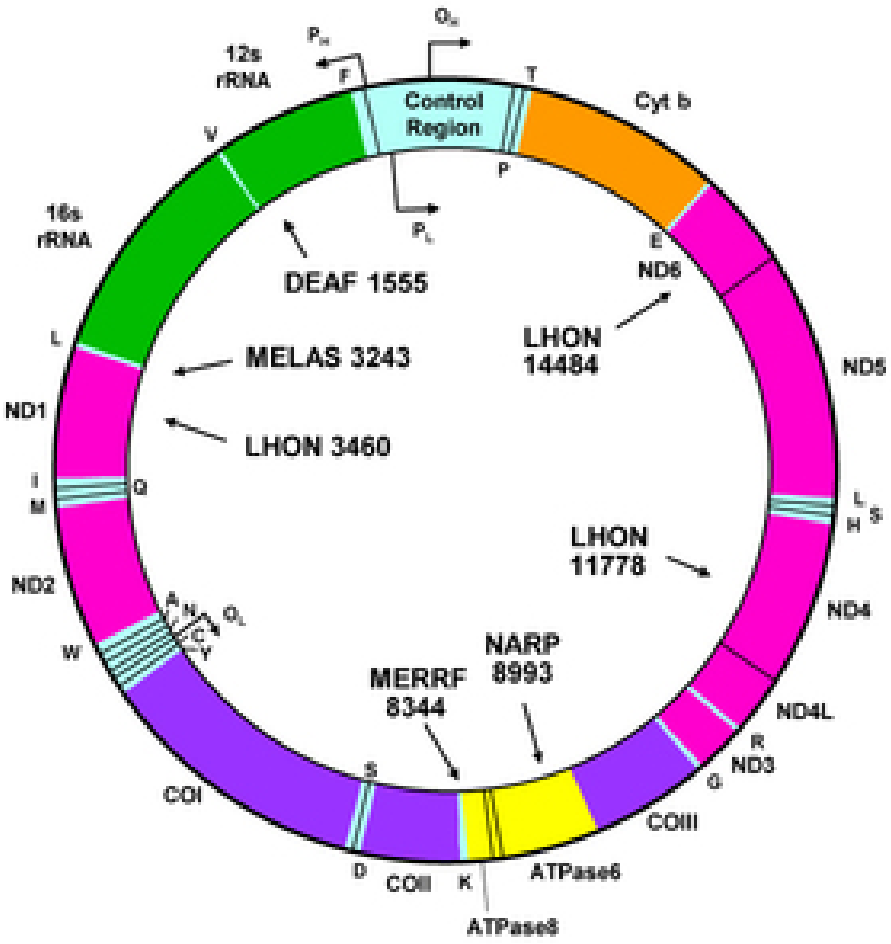
other disorders

About 20 mutations in the *MT-TL1* gene have been reported, most of which change single nucleotides in the gene. These mutations are associated with a variety of signs and symptoms chiefly affecting the muscles and nervous system. People with *MT-TL1* mutations often have muscle weakness, pain, and extreme fatigue, particularly during exercise (exercise intolerance). In some cases, the heart muscle is also weakened, which is known as cardiomyopathy. This abnormality prevents the heart from pumping normally.

A few children with changes in the *MT-TL1* gene have experienced delayed development, psychiatric problems, or developmental disorders that affect communication and social interaction (autistic spectrum disorders). *MT-TL1* mutations also have been identified in a small number of cases of sudden infant death syndrome (SIDS), which is a major cause of death in children younger than 1 year.

Chromosomal Location

Molecular Location: base pairs 3,230 to 3,304 on mitochondrial DNA (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Other Names for This Gene

- MTTL1
- tRNA leucine 1 (UUA/G)

Additional Information & Resources

Educational Resources

- Basic Neurochemistry (sixth edition, 1999): Diseases of Mitochondrial Metabolism
  https://www.ncbi.nlm.nih.gov/books/NBK27914/
- Madame Curie Bioscience Database: Mitochondrial Translation System
  https://www.ncbi.nlm.nih.gov/books/NBK6292/#A27945
- Mayo Clinic Mitochondrial Disease Biobank
  http://www.mayo.edu/research/centers-programs/mitochondrial-disease-biobank/overview
- Molecular Biology of the Cell (fourth edition, 2002): How Cells Obtain Energy from Food
  https://www.ncbi.nlm.nih.gov/books/NBK26882/#A289
- Molecular Cell Biology (fourth edition, 2000): Mitochondria are the Principal Sites of ATP Production in Aerobic Cells
  https://www.ncbi.nlm.nih.gov/books/NBK21743/#A1189
- Neuromuscular Disease Center, Washington University: MELAS
  http://neuromuscular.wustl.edu/mitosyn.html#melas
- Neuromuscular Disease Center, Washington University: MERRF
  http://neuromuscular.wustl.edu/mitosyn.html#merrf
- The Cell: A Molecular Approach (second edition, 2000): The Genetic System of Mitochondria
  https://www.ncbi.nlm.nih.gov/books/NBK9896/#A1629

GeneReviews

- MELAS
  https://www.ncbi.nlm.nih.gov/books/NBK1233
- MERRF
  https://www.ncbi.nlm.nih.gov/books/NBK1520
- Mitochondrial Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1224
- Mitochondrial DNA Deletion Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1203

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28MT-TL1%5BTIAB%5D%29+OR+%28%28MTTL1%5BTIAB%5D%29+OR+%28tRNA+leucine+1%5BTIAB%5D%29%29+OR+%28A3243G%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- SUDDEN INFANT DEATH SYNDROME
  http://omim.org/entry/272120
- TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 1
  http://omim.org/entry/590050

Research Resources

- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MT-TL1%5Bgene%5D
- HGNC Gene Family: Mitochondrially encoded tRNAs
  http://www.genenames.org/cgi-bin/genefamilies/set/843
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=7490
- Mitomap: rRNA/tRNA mutations
  http://www.mitomap.org/MITOMAP/MutationsRNA
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4567

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